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Emergency revascularization in patients with cardiogenic shock on admission: a report from the SHOCK trial and registry

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Aims To determine clinical correlates and optimal treatment strategy in patients with cardiogenic shock (CS) on admission.
Methods and results In SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK? (SHOCK) trial and registry patients with left ventricular (LV) dysfunction ($n = 1053$), CS on admission occurred in 26% of directly admitted patients ($n = 166/627$). Time from myocardial infarction to CS was shorter, initial haemodynamic profile poorer, and aggressive treatment less frequent in CS on admission than in delayed CS patients. CS on admission patients constituted a smaller relative proportion (11%) of the transferred ($n = 48/426$) when compared with the directly admitted cohort ($P < 0.001$). In-hospital mortality was higher (75 vs. 56%; $P < 0.001$) with more rapid death (24-h mortality 40 vs. 17%; $P < 0.001$) in CS on admission than in delayed CS patients. Emergency revascularization reduced in-hospital mortality in CS on admission (60 vs. 82%; $P = 0.001$) and in delayed CS patients similarly (46 vs. 62%; $P < 0.001$; interaction $P = 0.25$). After adjustment for clinical differences, CS on admission was an independent predictor of in-hospital mortality ($P = 0.008$).
Conclusion CS on admission patients have a worse outcome but benefit equally from emergency revascularization as delayed CS patients, emphasizing the need for rapid and direct access of CS on admission patients to facilities providing this care.

Introduction

Cardiogenic shock (CS) complicates acute myocardial infarction (AMI) in up to 10% of cases and remains the most common cause of in-hospital death from AMI because of high mortality rates.[1] In up to one-quarter of the cases, CS is already present when the patient arrives at the admitting hospital.[2–8] Care for this precipitously ill subgroup of patients presenting with CS on admission is challenging because of their severe haemodynamic compromise from the outset and the expected high complication rates.

In a population with CS due to left ventricular (LV) failure, emergency revascularization supported by intra-aortic balloon counterpulsation has been tested in a randomized trial and showed considerable survival benefit with an absolute mortality reduction of 13% after 1 year when compared with initial medical stabilization.[9] However, it is unclear whether angiography and subsequent revascularization in the critically ill and rapidly deteriorating patients with CS on admission is safe and effective, or futile.[10] If a clear benefit from an aggressive approach can be shown in patients with CS on admission, they should undergo emergency revascularization and intra-aortic counterpulsation, and, thus, should directly be admitted to pre-defined regional specialized shock centres capable of emergency cardiac catheterization and percutaneous or surgical revascularization.[11]

Thus, we examined the SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? (SHOCK) trial and registry[9,12,13] to investigate the incidence, clinical characteristics, optimal therapeutic management, and outcome of CS on admission in patients with CS complicating AMI.

Methods

SHOCK trial and registry

This is a pre-specified subgroup analysis of the SHOCK trial and registry. Details of the SHOCK trial design and eligibility criteria have been published previously.[12,14] In brief, the SHOCK trial is a multicentre international randomized trial comparing the treatment

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strategies of emergency revascularization and initial medical stabilization in CS complicating AMI. The protocol was approved by the local institutional review board at every site. Written informed consent was obtained by either the patient or a surrogate. Enrolled patients had CS onset within 36 h post-AMI and were randomized within 12 h of CS onset to either emergency revascularization or initial medical stabilization. Patients assigned to the emergency revascularization group had angioplasty or coronary artery bypass graft surgery as early as possible and within 6 h after randomization. In the initial medical stabilization group, fibrinolytic therapy was strongly recommended, and delayed revascularization ($\geq$54 h after randomization) was allowed, if clinically indicated. Intra-aortic balloon counterpulsation was recommended for all patients.

Patients who had suspected CS but did not meet all inclusion criteria, were outside the specified time windows, were unable or refused to give consent, or had an exclusion criterion were enrolled in the SHOCK registry.[13] In these patients, treatment was left at the discretion of the treating physicians, and follow-up was limited to the hospitalization period. One-year follow-up for trial patients were analysed in this report but was not available for registry patients.

Patients and definitions

To obtain a more homogeneous population, only patients with CS due to predominant LV failure were included in this analysis, i.e. patients with severe valvular disease such as acute severe mitral regurgitation or aortic stenosis, mechanical complications such as ventricular rupture or tamponade, isolated right ventricular infarction, known dilated cardiomyopathy, CS resulting from excess beta- or calcium-channel blockade, or a complication of a cardiac catheterization were excluded. Patients were analysed using their clinical status at admission to the initial hospital, and by treatment received.

Trial patients were analysed in combination with the registry patients (total cohort), whereas a separate analysis was performed restricted to the trial patients to assess the effect of emergency revascularization based on randomized treatment assignment. The total cohort consisted of 1491 patients, of whom 314 (21%) had CS owing to factors other than predominant LV failure and 124 (8%) had missing information about clinical status at admission, leaving 1053 (71%) patients for analysis (*Figure 1*). The SHOCK trial subset consisted of 302 patients, of whom eight (3%) had CS owing to factors other than predominant LV failure and 31 (10%) had missing information about clinical status at admission, leaving 263 (87%) patients for analysis. For all patients, a revascularization attempt $\leq$18 h after CS was defined as emergency revascularization, whereas a revascularization attempt $>$18 h after CS or not at all was defined as no/late revascularization according to the SHOCK trial's time eligibility criteria. Patients in whom CS onset was earlier or equal to the time of initial hospital admission were classified as having CS on admission. Survival for the total cohort was defined as time from original admission to discharge.

Statistical analysis

Categorical variables were compared using Fisher's exact test. Continuous variables were compared using Student's *t*-test for normally distributed variables and Wilcoxon rank-sum test for non-normally distributed variables. Descriptive statistics were presented as means $\pm$SD, as medians with inter-quartile ranges, or as percentages. The interaction between emergency revascularization and admission status were tested for categorical variables by logistic regression modelling and for continuous variables by analysis of variance (ANOVA) between groups. The covariate-adjusted association between in-hospital mortality and CS on admission was assessed by multivariate logistic regression, in a first step, considering all clinical variables significant in univariate analysis at $P < 0.20$, e.g. admission status (transfer vs. direct admission), anoxic brain

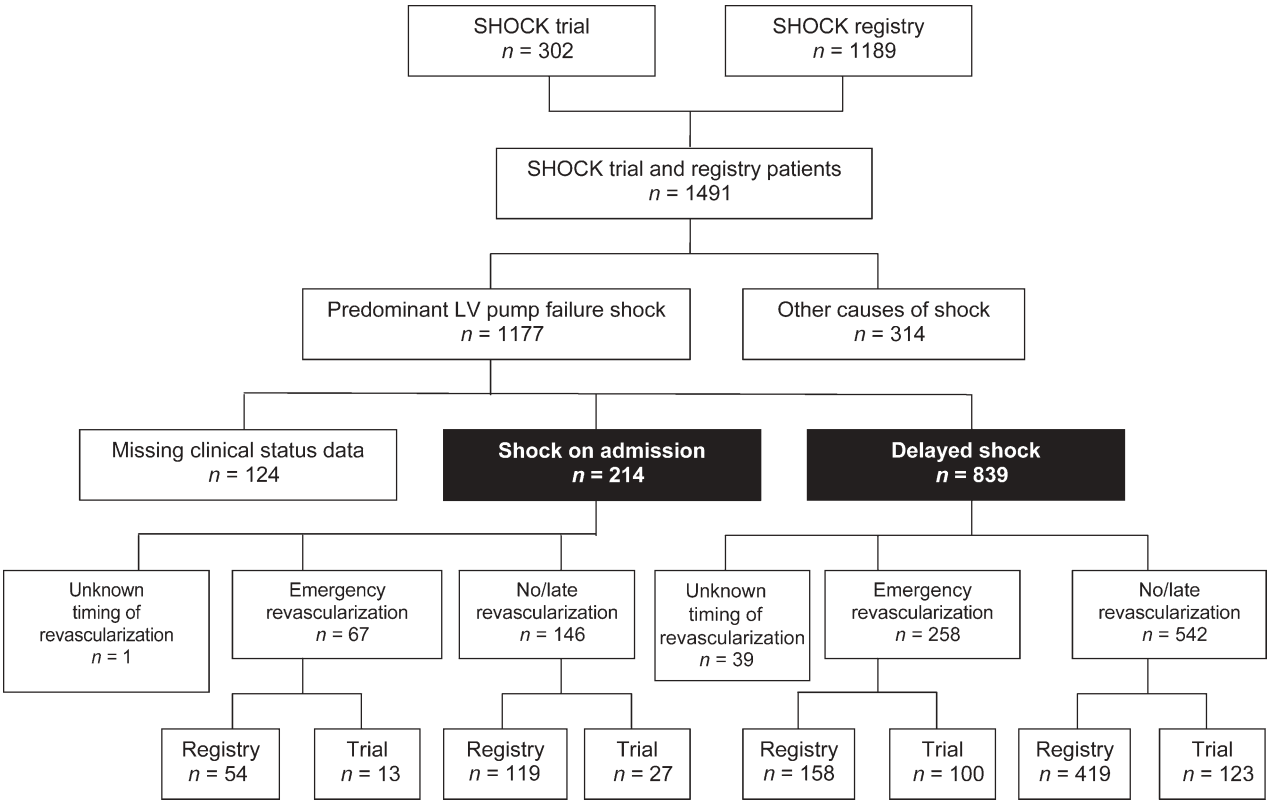

Figure 1 Flowchart of patient sample.

damage, peripheral hypoperfusion, heart rate, systolic blood pressure, and lowest systolic blood pressure, retaining all variables with a significance level of $P < 0.05$ in the multivariate model. In a second step, the association between in-hospital mortality and CS on admission was additionally adjusted using variables assessed by right heart catheterization considering all variables significant in univariate analysis at $P < 0.20$, i.e. cardiac power index and stroke work index. The Kaplan–Meier method and log-rank test were used to estimate and compare survival curves. All *P*-values are two-sided and considered statistically significant if ≤ 0.05.

Results

Patient sample

The total cohort included 1053 patients, of whom 214 (20%) had CS on admission and 839 (80%) developed CS during hospitalization. Among 627 direct admit patients, 166 (26%) had CS on admission compared with 48 (11%) of 426 patients transferred from outlying hospitals ($P < 0.001$).

Baseline characteristics

Patients with CS on admission had a shorter period between AMI and CS onset than patients with delayed CS, a higher rate of CS onset <6 h after AMI and a lower rate of transfer admissions, but were otherwise similar regarding baseline demographic variables. Peripheral hypoperfusion and anoxic brain damage occurred more often in patients with CS on admission than in delayed CS patients (*Table 1*). Patients with CS on admission had a poorer initial haemodynamic profile than patients with delayed CS, with lower systolic blood pressure and stroke work index but similar cardiac index, pulmonary capillary wedge pressure (PCWP), systemic vascular resistance, and LV ejection fraction (EF) (*Table 2*).

Treatment

Patients with CS on admission less often received fibrinolytic therapy, intra-aortic balloon counterpulsation, pulmonary artery catheterization, cardiac catheterization, revascularization, and coronary artery bypass surgery, but were mechanically ventilated more often when compared with patients who developed CS during hospitalization (*Table 3*). These differences were driven by the registry cohort, as trial patients per protocol received similar treatment. The cardiac catheterization rate was lower in patients with CS on admission than in patients with delayed CS, largely because of fewer angiograms in the no/late revascularization patients likely as a result of excess early deaths.

Mortality and effect of emergency revascularization on outcome

The in-hospital mortality rate in the total cohort was higher in patients with CS on admission (160/214, 75%) than in patients with delayed CS (470/839, 56%; $P < 0.001$; *Figure 2*). After adjustment for clinical variables that differed between the CS on admission and delayed CS groups, i.e. admission status, anoxic brain damage, peripheral hypoperfusion, and systolic blood pressure, CS on admission was still independently associated with in-hospital mortality ($n = 899$, odds ratio 1.68, 95% confidence interval 1.14–2.46; $P = 0.008$). However, after adjustment for stroke work index, CS on admission was no longer significant in the

Table 1 Baseline characteristics

	Shock on admission ($n = 214$)	Delayed shock ($n = 839$)	*P*
Age (years)	68.3 ± 11.9	68.1 ± 11.8	0.777
Sex (male, %)	143 (66.8)	534 (63.7)	0.424
White race (%)	163 (77.3)	690 (82.6)	0.074
Transfer admission (%)	48 (22.4)	378 (45.1)	<0.001
History of hypertension (%)	105 (52.5)	418 (51.4)	0.813
Diabetes (%)	69 (33.5)	267 (32.4)	0.803
Hypercholesterolaemia [$n = 552$, (%)]	39 (38.6)	179 (39.7)	0.911
History of smoking [$n = 900$, (%)]	80 (48.5)	385 (52.4)	0.389
Prior myocardial infarction (%)	88 (42.5)	313 (38.5)	0.301
Prior PCI (%)	11 (5.5)	60 (7.3)	0.440
Prior coronary artery bypass graft surgery (%)	15 (7.3)	83 (10.0)	0.287
Prior congestive heart failure (%)	39 (19.5)	127 (15.7)	0.201
Prior renal failure (%)	15 (7.4)	76 (9.5)	0.413
Median creatinine clearance (mL/min) ($n = 690$)	49.5 (22.8,67.0)	51 (31.4,72.1)	0.307
Median time MI to CS (h)	1.5 (0.5,4.1)	8.1 (2.8,21.0)	<0.001
Time MI to CS <6 h (%)	154 (79.0)	341 (41.8)	<0.001
Median highest total CPK (U/L) ($n = 991$)	2342 (516,4660)	2281 (834,4623)	0.501
CPR (%) ($n = 211$)	10 (29.4)	37 (20.9)	0.269
VT or VF (%) ($n = 212$)	9 (26.5)	41 (23.0)	0.663
Anoxic brain damage (%)	14 (6.9)	13 (1.6)	<0.001
Peripheral hypoperfusion (%) ($n = 989$)	197 (97.5)	734 (93.3)	0.019

Continuous data are presented as mean ±SD; skewed continuous data are presented as median (first, third quartile). Data are presented as number of patients with percentages unless defined otherwise. All variables without given sample size have <5% missing data. MI, myocardial infarction; CPK, creatine phosphokinase; CPR, cardiopulmonary resuscitation prior to enrolment; VT, ventricular tachycardia prior to enrolment; VF, ventricular fibrillation prior to enrolment.

Table 2 Baseline haemodynamic, echocardiographic, and angiographic variables

	Shock on admission ($n = 214$)	Delayed shock ($n = 839$)	P
Heart rate (b.p.m.)[a]	93.8 ± 27.1	97.0 ± 24.7	0.104
SBP (mmHg)[a]	84.1 ± 27.2	89.0 ± 21.1	0.017
Lowest SBP (mmHg) ($n = 770$)	64.2 ± 19.0	68.7 ± 14.8	0.008
DBP (mmHg)[a] ($n = 886$)	51.6 ± 20.7	53.6 ± 16.3	0.241
PCWP (mmHg)[a] ($n = 703$)	24.9 ± 8.3	23.8 ± 8.2	0.196
Cardiac index (L/min/m^2)[a] ($n = 590$)	1.86 ± 0.70	1.96 ± 0.73	0.206
Median CPI (W/m^2)[a] ($n = 536$)	0.25 (0.21,0.33)	0.28 (0.21,0.36)	0.178
SVRI (dynes sec/cm^5/m^2)[a] ($n = 360$)	2503 ± 1177	2464 ± 1084	0.812
Stroke work index (gm/m^2)[a] ($n = 360$)	9.3 (6.9,11.9)	11.5 (7.9,16.3)	0.020
Ejection fraction (%)[a,b] ($n = 289$)	34.3 ± 14.4	31.4 ± 13.0	0.212
Number of diseased vessels ($n = 651$)			0.549
0/1 (%)	21 (21.0)	97 (17.6)	
2 (%)	23 (23.05)	115 (20.9)	
3(%)	56 (56.0)	339 (61.5)	
Culprit vessel ($n = 540$)			0.102
Left main (%)	8 (9.9)	28 (6.1)	
Left anterior descending (%)	31 (38.3)	224 (48.8)	
Left circumflex (%)	14 (17.3)	65 (14.2)	
Right (%)	26 (32.1)	140 (30.5)	
Saphenous vein graft (%)	2 (2.5)	2 (0.4)	

Continuous data are presented as mean ±SD; skewed continuous data are presented as median (first, third quartile). Data are presented as number of patients with percentages unless defined otherwise. All variables without given sample size have <5% missing data.

[a]Obtained while on support measures.

[b]Obtained by echocardiography and angiography. CPI, cardiac power index.

Table 3 Therapeutic management

	Shock on admission			Delayed shock			P
	All[a] ($n = 214$)	Emergency revascularization ($n = 67$)	No/late revascularization ($n = 146$)	All[a] ($n = 839$)	Emergency revascularization ($n = 258$)	No/late revascularization ($n = 542$)	
Ventilator (%)	177 (82.7)	59 (88.1)	117 (80.1)	639 (76.2)	216 (83.7)	396 (73.1)	0.044
Pulmonary artery catheterization (%)	131 (61.2)	52 (77.6)	78 (53.4)	610 (72.7)	212 (82.2)	367 (67.7)	0.001
Vasopressor/inotropes (%) ($n = 850$)	158 (99.4)	54 (98.2)	104 (100)	679 (98.3)	223 (98.7)	425 (98.2)	0.481
IABC (%)	111 (51.9)	56 (83.6)	54 (37.0)	512 (61.0)	221 (85.7)	263 (48.5)	0.016
Fibrinolytic therapy (%)	63 (29.4)	22 (32.8)	41 (28.1)	357 (42.7)	103 (39.9)	242 (44.8)	<0.001
Coronary angiography (%)	108 (50.5)	66 (98.5)[b]	41 (28.1)	571 (68.1)	256 (99.2)[b]	277 (51.1)	<0.001
Revascularization (%)	84 (39.3)	67 (100)[a]	16 (11.0)	410 (48.9)	258 (100)†	113 (20.9)	0.014
Revascularization timing ($n = 453$)							0.044
Emergency revascularization (%)	67 (80.7)	67 (100)	—	258 (69.5)	258 (100)	—	
No/late revascularization (%)	16 (19.3)	—	16 (100)	113 (30.5)	—	113 (100)	
PCI (%)	69 (32.2)	61 (91.0)[c]	7 (4.8)[c]	270 (32.2)	191 (74.0)[c]	46 (8.5)[c]	1.000
CABG (%)	18 (8.4)	9 (13.4%)	9 (6.2)	161 (19.2)	83 (32.2)	70 (12.9)	<0.001

Data are presented as number of patients with percentages. All variables without given sample size have <5% missing data.

IABC, intra-aortic balloon counterpulsation; CABG, coronary artery bypass graft surgery.

[a]Forty patients had insufficient data to classify as emergency or no/late revascularization.

[b]Three patients had coronary angiography immediately before shock onset without being repeated after shock onset.

[c]Interaction of shock on admission vs. delayed shock and emergency revascularization vs. no/late revascularization, $P < 0.001$.

subset of patients with data available ($n = 347$, odds ratio 1.25, 95% confidence interval 0.66–2.37; $P = 0.495$). There was no significant interaction between emergency revascularization and admission status for in-hospital mortality ($P = 0.25$ for interaction), indicating a similar treatment effect in both groups. Patients undergoing emergency revascularization had a lower mortality rate than those with no/late revascularization in both the CS on admission (40/67,

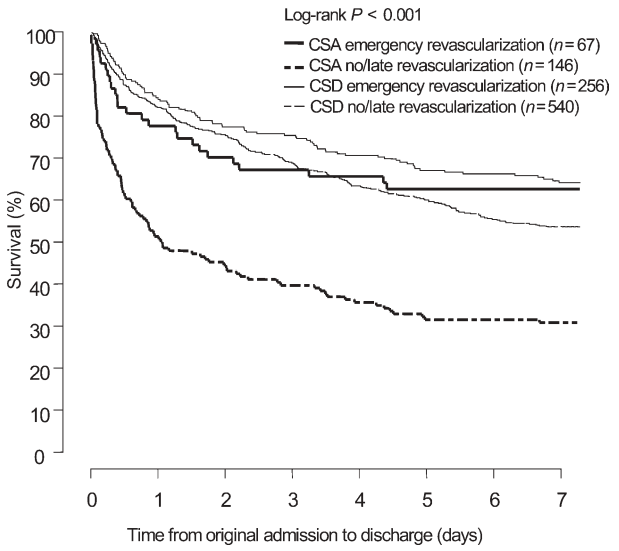

Figure 2 Estimated 7-day survival by timing of shock and treatment received for the total cohort ($n = 1009$). Patients who received emergency revascularization (solid lines) had fewer deaths than those who had no/late revascularization (dashed lines), both among those with shock on admission (heavy lines) and those who developed shock (light lines). CSA, cardiogenic shock on admission; CSD, delayed cardiogenic shock.

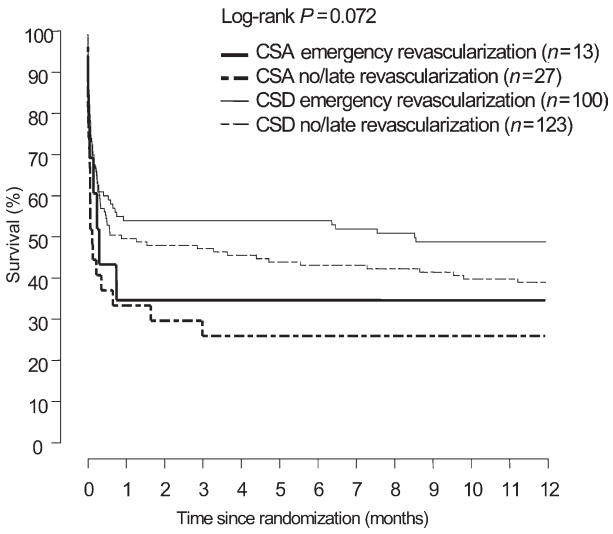

Figure 3 One-year survival by timing of shock and treatment received for the SHOCK trial cohort ($n = 263$). As in the total cohort, patients who received emergency revascularization benefited, regardless of shock status on admission. CSA, cardiogenic shock on admission; CSD, delayed cardiogenic shock.

60% vs. 119/146, 82%; $P = 0.001$) and delayed CS groups (118/258, 46% vs. 338/542, 62%; $P < 0.001$). In the overall group, mortality at 24 h was higher in patients with CS on admission than in delayed CS patients (86/213, 40% vs. 139/837, 17%; $P < 0.001$).

To determine the effect of emergency revascularization on outcome in patients with CS already present on admission to the outlying hospitals and subsequently transferred to a centre capable of revascularization, the CS on admission cohort was classified by directly admitted vs. transferred patients. Emergency revascularization was associated with lower in-hospital mortality in both directly-admitted (31/53, 59% vs. 94/112, 84%; $P < 0.001$) and transferred (9/14, 64% vs. 25/34, 74%; $P = 0.73$) patients with CS on admission ($P = 0.26$ for interaction); however, the latter difference was not significant, probably because of a small sample size.

SHOCK trial cohort

The trial analysis cohort included 263 patients, of whom 40 (15%) had CS on admission and 223 (85%) had CS developing during hospitalization. Among 132 directly admitted trial patients, 31 (23%) presented with CS on admission when compared with nine (7%) of 131 patients transferred from outlying hospitals ($P < 0.001$).

Baseline differences between patients with CS on admission and delayed CS in the trial were similar to those in the total cohort (data not shown). Despite protocol-directed care, trial patients with CS on admission had a higher in-hospital mortality than those with delayed CS (26/40, 68% vs. 108/223, 49%; $P = 0.039$). Mortality rates at 30 days (26/40, 65% vs. 108/223, 48%; $P = 0.060$) and 1 year (29/40, 73% vs. 127/222, 57%; $P = 0.081$) tended to be higher in patients with CS on admission when compared with patients with delayed CS, respectively (*Figure 3*). There was no significant interaction between emergency revascularization and admission status for mortality either at 30 days ($P = 0.87$ for interaction) or 1 year ($P = 0.85$ for interaction).

Discussion

Our study shows that shock is diagnosed at hospital arrival in as much as 26% of CS patients directly admitted to centres capable of cardiac catheterization and revascularization. Patients with CS on admission develop shock more rapidly following AMI, have higher rates of anoxic brain damage and peripheral hypoperfusion, display a worse initial haemodynamic profile, undergo fewer invasive procedures, and suffer higher mortality than in patients with delayed CS. After adjustment for important clinical baseline differences, CS on admission is highly significantly associated with in-hospital mortality, although this association disappears after inclusion of right heart catheterization data, specifically stroke work index, into the model. Despite their precipitous critical condition, patients with CS on admission benefit equally from emergency revascularization as in patients with delayed CS. Together, these observations emphasize the need for patients with CS on admission to be recognized and admitted expeditiously to facilities capable of emergency invasive assessment and definitive revascularization.

Proportion of shock on admission

Concordant with our findings, CS on admission has been observed in up to one-quarter of patients in large CS registries and trials.[2–8] However, in our study, the proportion of CS on admission was higher among directly admitted than in transferred patients probably because of a selection bias in the latter, i.e. patients with CS on admission to community hospitals likely died too soon to be transferred than the patients who developed CS during their hospitalization. Thus, the higher proportion of CS on admission in directly admitted patients may better reflect the real-world situation. In contrast, the fact that many patients developed

CS directly after treatment initiation and that the median time between AMI and CS in patients with delayed CS was more than 8 h raises the concern that iatrogenic factors, e.g. drugs such as morphine, beta-blockers, ACE-inhibitors, nitrates, and diuretics alone or in combination, may have contributed to the development of severe hypotension and, subsequently, shock.[15,16]

Mortality and timing of death

Several large studies performed in both tertiary care centres and community hospitals showed similar mortality rates for patients with CS on admission and delayed CS,[3,6,7] whereas others reported lower mortality rates in CS on admission.[5,17] This contrasts with our observation that patients with CS on admission had higher in-hospital mortality rates than those with delayed CS, but can be explained by possible discrepancies in design (prospective vs. retrospective data collection), CS definition, inclusion and exclusion criteria (mechanical complications of AMI), transfer rates, and treatment between the different studies. However, in our study, the mortality rate for patients with CS on admission might even be underestimated because death occurred much more rapidly in patients with CS on admission than in delayed CS; the mortality rate in the first 24 h among patients with CS on admission was more than double the rate of patients with delayed CS. Because of this rapid deterioration, it can be hypothesized that some patients with CS on admission presenting to hospitals without catheterization capabilities die before reaching the specialized centre. This is supported by the finding that the proportion of CS on admission among patients transferred from outlying hospitals was less than half among directly-admitted patients, as discussed earlier.

Effect of emergency revascularization

The use of an invasive treatment strategy in the setting of CS has been studied in both retrospective analyses[5,18–24] and randomized controlled trials[9,12,25] and showed a beneficial effect of emergency revascularization on outcome. However, given their poor haemodynamic situation at hospital arrival and their rapid deterioration, patients with CS on admission are not likely to undergo cardiac catheterization and revascularization. This was confirmed in our study by the finding that patients with CS on admission received fewer invasive procedures than in patients with CS developing during the hospitalization. However, the survival benefit from emergency revascularization was similar in both CS on admission and delayed CS groups. Although patients with CS on admission had a poorer initial haemodynamic profile than the patients with delayed CS, they were of similar age and had similar cardiovascular risk factors, LVEF, and extent of diseased vessels (among those who underwent angiography). It can be hypothesized that mechanisms other than more severe structural damage may play a role in the rapid clinical deterioration of patients with CS on admission following AMI, i.e. a more intense and rapid systemic inflammatory response, leading to greater haemodynamic derangement.[26]

Given the rapid clinical deterioration and the beneficial effect of emergency revascularization in CS on admission, our findings imply that patients arriving at the hospital in CS should receive reperfusion therapy, preferably percutaneous coronary intervention (PCI), as soon as possible. In addition, transfer protocols of emergency medical services should include the direct transport of patients with AMI complicated by CS to facilities capable of cardiac catheterization and revascularization as outlined in current guidelines.[11] In case of pre-hospital transport, patients with CS on admission should be transported directly to specialized centres, whereas in case of initial presentation to primary care hospitals, transfer to centres capable of revascularization should occur immediately. Following the example of regional trauma centres,[27] designated regional shock centres could prove invaluable in reducing mortality from CS.

Limitations

This database study is subject to inherent limitations. The mortality rate for patients with CS on admission might be underestimated as discussed earlier. Furthermore, the true proportion of patients with CS on admission can only be estimated from the direct admissions to the specialized centres capable of cardiac catheterization and revascularization. This rate may be different at primary care hospitals. Although our results suggest a more profound myocardial dysfunction in patients with CS on admission, we do not have mitral regurgitation grades or ventricular size on most patients to further assess the reason for the lower stroke work index.

Conclusion

CS on admission is associated with rapid and profound haemodynamic deterioration that is more severe than in delayed CS. This might explain the particularly poor early and late outcome in this precipitously ill subgroup. However, despite the gravity of illness with CS on admission, these patients benefit substantially from emergency revascularization. Thus, patients with CS on admission need immediate access to invasive assessment and definitive revascularization by PCI or coronary artery bypass graft surgery. Emergency medical services should, by protocol, rapidly identify and transport patients with CS on admission to pre-specified regional shock centres capable of providing this care.

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Conflict of Interest: none declared.

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